Category

Synthesis of Natural Products and Potential Drugs

Key words

glecaprevir

S_NAr reaction

intramolecular nucleophilic substitution

macrocyclization

cycloetherification

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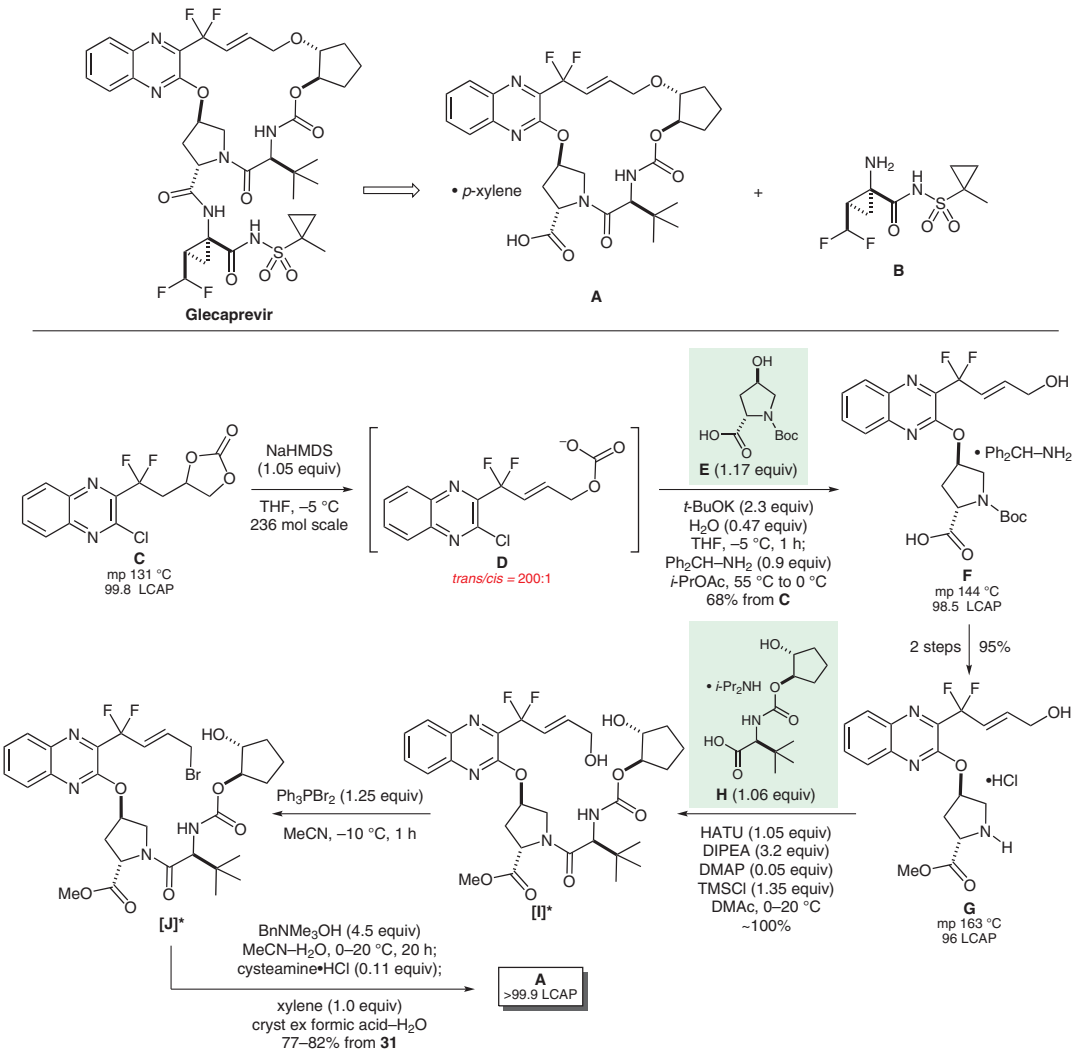
Development of a Large-Scale Route to Glecaprevir: Synthesis of the Macrocycle via Intramolecular Etherification
Org. Process Res. Dev. **2020**, *24*, 1373–1392, DOI: 10.1021/acs.oprd.0c00244.

Synthesis of Glecaprevir. Part 1



Significance: The combination of glecaprevir and pibrentasvir was approved in 2017 for the treatment of chronic hepatitis C virus infections. A new large-scale synthesis of glecaprevir is described in two parts. Part 1 shown here concerns the construction of the 18-membered macrocycle **A** featuring as the key step an intramolecular cycloetherification of allylic bromide **J**. For part 2, see *Org. Process Res. Dev.* **2020** *24*, 1393; *Synfacts* **2020**, *16*, 1259.

Comment: The identification of solvates with low solubility allowed the crystallization of macrocycle **A** in high purity directly from the reaction mixture. The overall yield to macrocycle **A** was 20% for the lowest yielding sequence through carbamate **H**, a significant improvement on the 15% yield of the enabling route based on ring-closing metathesis (*Org. Process Res. Dev.* **2020**, *24*, 183).

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